hypothesize that allostery in thrombin may instead occur through a primarily entropic mechanism.
To investigate the potential for entropic allostery in thrombin a series of accelerated molecular dynamics (AMD) simulations were performed. AMD applies a bias energy to the underlying potential of a classic MD system to model longer timescales on which allosteric events are more likely to occur. Residue by residue cross-correlation analysis and community network models constructed from the resulting trajectories are indicative of an allosteric pathway between the thrombin active site and TM4. In addition, order parameters back-calculated from trajectories of apo and TM bound thrombin, show differential dynamics near the thrombin active site and TM binding site. Together these results show that TM binding alters thrombin dynamics in a manner that could reasonably contribute to the observed change in specificity through entropic allostery.

3733-Pos Board B594
Computational Studies of a pH Responsive Histidine-Modified Cardiac Troponin I
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Cardiac troponin I (cTnI) functions as the molecular switch of the thin filament. Studies have shown that a A164H button engineered into cTnI enhances inotropic function under pathophysiological challenges. In vitro studies of myofilament calcium sensitivity and sarcomere shortening kinetics in intact and permeablized myocytes at baseline (pH 7.4) indicated similar cellular contractile function and myofilament calcium sensitivity between myocytes expressing wildtype cTnI and cTnI A164H while A164R showed a hypercontractile phenotype associated with increased myofilament calcium sensitivity. Under acidic conditions, compared to depressed function in myocytes with wildtype cTnI, myocytes expressing cTnI A164H maintained myofilament calcium sensitivity and contractile performance comparable to the calcium sensitizer cTnI A164R. The role of histidine modified cTnI was assessed by molecular dynamics (MD) simulations and pKa calculations of the wildtype and histidine or arginine-modified cTnI (148-173): cTnC (1-90) complex. The simulations showed similar conformations between the wildtype and the deprotonated cTnI A164H variant. In contrast, simulations of protonated cTnI A164H and cTnI A164R showed diverse conformation changes, both of which included the formation of a cTnI His 164 and cTnC Glu 19 salt bridge. pKa calculations showed no significant pKa shift for all ionizable residues except for cTnI His 164 and cTnC Glu 19 when the salt bridge is formed. The data shed light into the potential mechanism of pH activation of cTnI A164H and the importance of electrostatic interactions in governing the biophysical adjustments in troponin function necessary for nuanced modulation of myofilament function in response to changes in the cytosolic milieu.

3734-Pos Board B595
Pressure-Induced Denaturation of Proteins Studied by Generalized-Ensemble Molecular Simulations
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The pressure dependence of several proteins has recently been studied both experimentally and theoretically. Some of the experiments showed that proteins are denatured under high pressure conditions. We would like to understand the molecular mechanism of the pressure-induced denaturation of proteins by using molecular dynamics simulations.
Molecular dynamics simulations have been widely used for studying biomolecular systems. However, the molecular simulations of biomolecular systems often get trapped in local minimum energy states. One way to overcome such a difficulty is to use generalized-ensemble algorithms. Using generalized-ensemble algorithms in molecular simulations, we can sample protein conformations efficiently and calculate physical quantities accurately. We have recently developed a generalized-ensemble algorithm for the isobaric-isothermal ensemble. This method can be used to calculate accurate temperature and pressure dependence of biomolecular systems.
In this study we performed molecular simulations of ubiquitin, which is denatured under high pressure conditions. We performed generalized-ensemble molecular dynamics simulations by the NAMD program package. In these simulations, we used one temperature value, 300 K, and one hundred pressure values in range from 1 bar to 10,000 bar.
We calculated the fluctuations of the distance between all pairs of amino acid residues. A large distance fluctuation of an amino acid pair means that increasing and decreasing pressure makes the amino acid residues move largely and therefore it is possible that local protein structure changes are induced with increasing and decreasing pressure. The amino acid residues which were largely displaced under high pressure conditions in the experiments correspond to the largely fluctuated amino acid residues in the molecular simulations.

3735-Pos Board B596
An Elastic Network Coarse Grained MD Model Tested on Protein with Hinge Movement upon Ligand Binding
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In recent years, coarse grained (CG) models, with a resolution at the residue level for proteins,[1,2] have gained great popularity, due to its balance between accessible time scale and detail level. However, because of the coarse description of the residues, electrostatic interactions arising from the electron distribution within the coarse grained beads are lost, and the model fails to consistently reproduce protein secondary and tertiary structure. Therefore additional restraints stabilizing the initial structure are imposed, allowing the CG model to maintain the correct structural scaffold,[3] but impairing the ability to study protein conformational changes.
Here I will present a study comparing the capability of selected CG models to describe the conformational change of a two-domain protein that undergoes fully closure upon ligand binding. With the proposed domELNEDIN model, where an elastic network is set up only internally in the protein domains, we are able to observe the expected conformational change. To also improve the description of the protein-ligand interaction in the CG model, representations of the ligand using bead types similar to those introduced recently for polarizable CG water[4] were tested.
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3736-Pos Board B597
Slow Dynamics in Protein Fluctuations Revealed by Time-Structure Based Independent Component Analysis
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Protein fluctuations in equilibrium are an important factor for its structural change and function. It has been found that a small number of low-frequency modes in a protein, determined by normal model analysis or principal component analysis, account for its large fluctuations and contribute to its structural change significantly. However, dynamical aspects of protein fluctuations and their roles in protein function remain unclear. Recently, we have proposed the time-structure based independent component analysis (tICA) to reveal slow dynamics of a protein [Y. Naritomi and S. Fuchigami, J. Chem. Phys. 134, 065101 (2011)]. In this paper, we focused on domain motions of the target protein by using rigid-body domain analysis. However, a protein shows not only domain motions but also a variety of motions of main- and side-chains. In the present study, we investigated protein main-chain dynamics on a long time scale by using all-atom molecular dynamics (MD) simulation and the tICA. As a target protein, we selected lysine-, arginine-, ornithine-binding protein (LAO), which undergoes a large structural change upon ligand binding. A one-microsecond MD simulation of apo-LAO in explicit water was performed using MARBLE and the CHARMM22/CMAP force field parameters. Applying the tICA to the simulation result yielded slow modes of the LAO, which represented both domain and local motions. Other analyses confirmed that these motions were actually occurred on the expected slow time scale, suggesting that the tICA is powerful for analyzing slow dynamics of proteins.

3737-Pos Board B598
Modulation Mechanism on the Conformational Diversities of Biantennary Complex-Type N-Glycans in Water
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The core fucosylation and the introduction of bisecting GlcNAc of N-glycans are known to modulate their conformations and considered as one of the fundamental means for regulating their binding affinities to lectins. In this presentation, we show details of the modulation mechanism, which was not fully elucidated in the past, by conducting replica-exchange molecular dynamics simulations of four distinct N-glycan molecules (Bi9, BiB10, BiF10 and BiBF11). The global conformation was highly correlated with the motion of 1-6 arm. The N-glycan without core fucosylation and the bisecting GlcNAc shows highest flexibility